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EP-A- 0 177 342
WO-A-82/00588
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US-A- 4 462 985
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Chemical Abstracts, vol. 103, no. 26, December 30, 1985, abstract no. 220810z, Columbus, Ohio, US

Acta Virol. (Czech), vol. 30, no. 2, 1986, pp. 161-169; L. Borecky

The Lancet, vol. 1, May 1979 (US), Kajander, pp. 984-985

J. Interferon Res., vol. 6, June 1986 (US), Yamamoto, pp. 143-152

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Description

This invention relates generally to an interferon composition in solid dosage form for providing low oral dosages of interferon. This invention also relates to the use of interferon in low dosages in the manufacture of medicaments to potentiate disease-corrective immune responses in warm-blooded vertebrates afflicted with immuno-resistant diseases characterized by apparent hyperactive or hypoactive immune system function.

"Interferon" is a term generically comprehending a group of vertebrate glycoproteins and proteins which are known to have various biological activities, such as antiviral, antiproliferative, and immunomodulatory activity at least in the species of animal from which such substances are derived. The following definition for interferon has been accepted by an international committee assembled to devise a system for the orderly nomenclature of interferons: "To qualify as an interferon a factor must be a protein which exerts virus nonspecific, antiviral activity at least in homologous cells through cellular metabolic processes involving synthesis of both RNA and protein." Journal of Interferon Research, 1, pp. vi (1980). "Interferon" as used herein in describing the present invention shall be deemed to have that definition.

Since the first descriptions of interferon by Isaacs and Lindeman [See, Proc. Roy. Soc. London (Ser. B), Vol. 147, pp. 258 et seq. (1957) and U.S. Patent No. 3,699,222], interferon has been the subject of intensive research on a worldwide basis. The literature is replete with publications concerning the synthesis of interferon, its proposed molecular characterizations, its clinical applications and proposed mechanisms of its antitumor, antiviral, and immune system activities.

Because of the intensity and disparate origins of research concerning interferon and its characteristics and uses, there exists a substantial lack of uniformity in such matters as classification of interferon types. There are also numerous, sometimes contradictory, theories concerning the mode of action of interferon in producing clinical effects.

Although originally isolated from cells of avian origin (chick allantoic cells), interferon production has been observed in cells of all classes of vertebrates, including mammals, amphibians, birds and reptiles. Interferon production by vertebrate cells is seldom spontaneous but is often readily "induced" by treatment of cells (in vivo or in vitro) with a variety of substances including viruses, nucleic acids (including those of viral origin as well as synthetic polynucleotides), lipopolysaccharides, and various antigens and mitogens.

Interferons have generally been named in terms of the species of animal cells producing the substance (e.g., human, murine, or bovine), the type of cell involved (e.g., leukocyte, lymphoblastoid, fibroblast) and, occasionally, the type of inducing material responsible for interferon production (e.g., virus, immune). Interferon has been loosely classified by some researchers according to induction mode as either Type I or Type II, with the former classification comprehending viral and nucleic acid induced interferon and the latter class including the material produced as a lymphokine through induction by antigens and mitogens. More recently, the international committee devising an orderly nomenclature system for interferon has classified interferon into types on the basis of antigenic specificities. In this newer classification, the designations alpha (α), beta (β), and gamma (γ) have been used to correspond to previous designations of leukocyte, fibroblast, and type II (immune) interferons, respectively. Alpha and beta interferons are usually acid-stable and correspond to what have been called type I interferons; gamma interferons are usually acid-stable and correspond to what has been called type II interferons. The international committee's nomenclature recommendations apply only to human and murine interferons. Journal of Interferon Research, 1 pp. vi (1980).

In its earliest applications, interferon was employed exclusively as an antiviral agent and the most successful clinical therapeutic applications to date have been in the treatment of viral or virus-related disease states. It became apparent, however, that exogenous interferon was sometimes capable of effecting regression or remission of various metastatic diseases. An overview of current clinical trials of interferon as an antiviral and antiproliferative therapeutic agent is contained in Interferon: In Vivo and Clinical Studies, Volume 4, Eds: N. B. Finter and R. K. Oldham, Academic Press, New York, 1985.

The clinical agent of choice for the present is human leukocyte interferon, "mass-produced" by procedures involving collection and purification of vast quantities of human buffy coat leukocytes, induction with virus, and isolation from culture media.

In the work described above, interferon has been administered parenterally, i.e., intramuscularly and intradermally, with some successful topical and intranasal usages having been reported. It has seldom been administered intravenously because of substantial adverse effects attributable to "contaminants" in crude and even highly purified isolates.

As discussed above, there has been a significant research effort directed to the evaluation of therapeutic effects of interferon for a wide variety of diseases having an auto-immuno-pathologic basis. Before applicant's first report of successful oral

administration of interferon in his U.S. Patent Application Serial No. 415,525 (now U.S. Patent 4,462,985), there was no recognition in the art of the potential offered by oral administration of interferon. The generally held belief was that interferon could not survive the digestive conditions of the upper alimentary canal.

Since applicant's first disclosure of the immunotherapeutic benefit achievable via oral administration of interferon of heterologous mammalian species, he has continued to investigate the efficacy of orally administered interferon. In U.S. Patent No. 4,497,795, issued February 5, 1985, applicant described and claimed the use of interferon administered oralty or via intravenous administration to stimulate appetite and feed efficiency of bovine and porcine species. More recently applicant has described in now pending U.S. applications the use of interferon at dosages less than 5 IU per pound (11 IU per kg) of body weight for increasing feed efficiency and food utilization in warm-blooded vertebrates, for preventing and treating shipping fever, and for enhancing vaccine efficiency.

Human alpha-interferon has been marketed under the trademark Agriferon (Registered Trade Mark) by Immunomodulator Laboratories, Inc. ("IML") of Stafford, Texas for veterinary use in Texas since February 1985. The product is sold for oral administration to cattle to promote growth and feed efficiency and to prevent or treat viral respiratory infections. IML began selling an alpha-interferon product for horses in 1986. Both products are sold under a license of the present inventors U.S. Patent 4,462,985.

Interferon contacting the oral and/or pharyngeal mucosa, in amounts of less than (5 IU/lb) 11 IU/kg of body weight per day is consistently effective to potentiate disease-corrective immune responses in vertebrates afflicted with immuno-resistant disease states characterized by apparent hyperactive or hypoactive immune system function. Treatment in accordance with the present invention has been shown to effect remission of neoplastic disease, hyperallergenicity, immuno-resistant or immuno-debilitating viral infections and autoimmune disorders characterized by chronic tissue degenerative inflammation.

The clinical agent of choice for use in accordance with the present invention is human leukocyte interferon (human alpha-interferon), "mass-produced" by procedures involving collection and purification of quantities of human buffy coat leukocytes, induction of interferon production with virus, and isolation of culture media. (See "Preparation of Human Alpha-Interferon" below.) Also acceptable for use in accordance with present invention are human alpha-interferon products produced by recombinant DNA technology and now commercially available from Schering-Plough [as Intron (Registered Trade Mark)] and Hoffmann-LeRoche [as Roferon (Registered Trade Mark)] and approved by the FDA for treatment (parenterally) of hairy cell leukemia of man. Such recombinant interferon products are believed to be particularly effective when used in combination. Gamma interferon is also available by recombinant technology and is presently undergoing clinical trials by Genentech and others. Fibroblast interferon (beta-interferon) can be prepared in accordance with Example 1 in applicant's U.S. Patent No. 4,462,985 issued July 31, 1984.

Interferon of human and murine origins has been quantified in the art in terms of International Units ("IU"). As used herein, a "unit" of interferon (to be distinguished from "IU") shall mean the reciprocal of a dilution of interferon-containing material that, as determined by assay, inhibits one-half the number of plaques of a challenge virus, the challenge virus being the vesicular stomatitis virus ("VSV"). So quantified a "unit" of interferon is routinely found to be about one-tenth the quantity of interferon represented by one "IU." In other words, for the purpose of defining the present invention, 1 unit ≈0.1 IU.

The present invention relates to compositions useful in the treatment of immuno-resistant disease states with interferon. The compositions may be used in the treatment of diseases in warm-blooded vertebrates, particularly certain diseases which the immune system of many species is poorly equipped to handle, as evidenced by either a lack of disease defeating response and/or an apparently misdirected immune response resulting in a chronic tissue degenerative inflammatory condition or other physical complications. While there has been a significant research effort directed to the use of interferon for treatment of such diseases, reported results, although positive overall, have been inconsistent. The principle reason for such inconsistency in view of my most recent research efforts is that earlier investigators have failed to define optimum dosage and route of interferon administration.

The present invention is based on applicant's discovery that interferon can be used as a consistently effective therapeutic agent for treatment of diseases having an immunopathologic basis - characterized by inadequate immune response and persistence of the disease or by an apparent hyperactive immune response resulting in tissue degenerative inflammatory conditions and related physical manifestations. Applicant has found that interferon, contacting the oral and pharyngeal mucosa in amounts from (0.01 to 5 IU/lb) 0.022 to 11 IU/kg of body weight per day, is consistently efficacious for the treatment of diseases to which the

immune system of many warm-blooded vertebrates does not effectively respond.

The invention also provides methods of manufacturing interferon compositions and also is directed to the use of interferon for the manufacture of medicaments.

The invention provides a composition comprising interferon and a pharmaceutically acceptable carrier therefor, in an effervescent tablet form adapted for dissolution in water to form a mouthwash or gargle formulation for human patient use for stimulating an immunotherapeutic response in said patient, said effervescent tablets containing 1 to 1500 IU of interferon.

The invention further provides a composition comprising interferon, starch and sucrose in a solid dosage form defined for buccal use by a human patient for stimulating an immunotherapeutic response in said patient, said solid dosage form comprising 1 to 1500 IU of interferon and a pharmaceutically acceptable carrier therefor, said solid dosage form adapted for dissolving in contact with saliva in the patient's mouth to release the interferon essentially for contact with the patient's oral and pharyngeal mucosa.

According to the invention there is provided a method of manufacturing an interferon composition in solid dosage form defined for dissolving in contact with saliva in a patient's mouth and releasing said interferon for contact essentially with the oral and pharyngeal mucosa of said patient to stimulate an immunotherapeutic response, characterized by combining 1 to 1500 IU of interferon and a pharmaceutically acceptable carrier therefor.

The invention resides in the use of interferon for the manufacture of a medicament in a solid dosage form defined for buccal use by a human patient, said solid dosage form adapted for dissolving in contact with saliva in the patient's mouth to release the interferon essentially for contact with the patient's oral and pharyngeal mucosa for stimulating an immunotherapeutic response in said patient, said solid dosage form comprising interferon and a pharmaceutically acceptable carrier therefor, and providing 0.022 to 11 IU of interferon per kg (0.01 to 5 IU/lb) of patient body weight.

Furthermore the invention resides in the use of interferon for the manufacture of a medicament in an effervescent tablet form adapted for dissolution in water to form a mouthwash or gargle formulation for human patient use for stimulating a immunotherapeutic response in said patient, said effervescent tablet providing on dissolution 0.022 to 11 IU of interferon per kg (0.01 to 5 IU/lb) of patient body weight.

Alpha interferon, derived from tissue culture or by recombinant DNA techniques, is a preferred therapeutic agent in accordance with this invention. Alpha interferon can be administered alone or in combination with beta interferon or gamma interferon.

It is critical that the interferon be administered in a dosage form adapted to assure maximum contact of the interferon with the oral and pharyngeal mucosa of the patient. Contact of interferon with the mucosa can be enhanced by maximizing residence time of the interferon in the oral or pharyngeal cavity. Thus, best results seem to be achieved when the patient is requested to hold the interferon in the mouth for a period of time. Contact of interferon with the oral and pharyngeal mucosa and thereafter with the lymphatic system of the treated patient is unquestionably the most efficient method for administering immunotherapeutic amounts of interferon.

Disease conditions treated in accordance with the present invention include apparent autoimmune disorders characterized by a chronic tissue degenerative inflammatory condition. Diseases so characterized include multiple sclerosis, rheumatoid arthritis, stomatitis, and lupus erythematosus.

Another disease condition responding to treatment in accordance with the present invention is neoplastic disease. Thus, treatment with interferon in accordance with the invention can alone or in combination with other drugs or therapy, help effect remission of cancers such as malignant lymphoma, melanoma, mesothelioma, Burkitt lymphoma and nasopharyngeal carcinoma and other neoplastic diseases, especially those of known or suspected viral etiology. Based on the results observed to date, it is believed that treatment with interferon in accordance with the invention will similarly help effect remission of Hodgkin's Disease and leukemia.

Other disease conditions responding to treatment with interferon in accordance with the present invention are infectious diseases of viral origin in human species. Significantly, viral infection typically exhibiting persistent resistance to treatment have shown a dramatic response to treatment with interferon in low doses contacting the oral and pharyngeal mucosa of infected patients.

Exemplary of human viral infections showing remarkable response to treatment with interferon in accordance with the present invention are infections of human rhinovirus (common cold), herpes simplex I virus (cold sores) and human papovavirus (warts). Based on treatment results to date, it is expected that contact of interferon at low dosage with the oral and pharyngeal mucosa will provide an effective treatment for Acquired Immune Deficiency Syndrome (AIDS) and disease conditions having the herpes simplex II virus as the causative agent. A patient experiencing a condition of viral myocarditis has responded favorably to treatment

with interferon in accordance with the invention. Warts often dissipate within six to eight weeks after initiating treatment with interferon in accordance with this invention.

Other afflictions responding to contact of low dosage interferon are hyperallergenic conditions such as asthma. One "side effect" noted by patients treated with interferon in accordance with this invention is improved skin complexion. Thus, administration of interferon in dosages of (0.01 to 5 IU/lb) 0.022 to 11 IU/kg of body weight per day is effective to treat acne, specifically and improve human skin complexion generally.

Further, stimulating the immune system by oral contact with low dosage interferon is believed to assist the body in fighting bacterial infection. Treatment with interferon in accordance with this invention alone or in combination with therapeutic amounts of antibiotics can be especially effective in knocking down infections of antibiotic resistant microorganisms.

Administration of interferon in accordance with the present invention is preferably continued until the symptoms of the disease condition being treated subside. This can range from a period of one day, for example, where a human rhinovirus is the disease causative agent, to a period of up to six months for treatment of neoplastic disease. Rheumatoid arthritis patients are pain free within 2 to 10 days of initiating, treatment.
However, treatment of that disease is preferably conducted by administration of interferon for up to three (3) months.

Daily dosage of interferon can be administered as a single dosage or, preferably, it is divided and administered in a multiple-dose daily regimen. A staggered regimen, for example one to three days treatment per week or month, can be used as an alternative to continuous daily treatment.

The present invention provides interferon in a solid dosage form such as a lozenges adapted to be dissolved upon contact with saliva in the mouth with or without the assistance of chewing. Such a unitary dosage form is formulated to release 1 to 1500 IU of interferon upon dissolution in the mouth for contact with the oral and pharyngeal mucosa. Thus a unitary dosage form of interferon can be prepared by art-recognized techniques for forming compressed tablets such as chewable vitamins. Similarly, interferon can be incorporated into starch-based gel formulations to form a lozenge which will dissolve and-release interferon for contact with the oral mucosa when held in the mouth. Solid unitary dosage forms of interferon of the present invention can be prepared utilizing art recognized dosage formulation techniques. The pH of such formulations can range from 4 to 8.5. Of course, in processing to such unitary dosage forms one should avoid heating a pre-dosage form formulation, after addition of interferon, above 50° Centigrade.

Preparation of Human Alpha-Interferon

Human alpha-interferon can be prepared through the following procedure, commonly referred to as the Cantell procedure. The process begins with packs of human leukocytes, obtained in this case from the Gulf Coast Regional Blood Center, Houston, Texas. The buffy coats in these packs are pooled into centrifuge bottles, and then are diluted with 0.83% ammonium chloride. The mixture is incubated for 15 minutes with intermittent shaking, and is then centrifuged for 20 minutes at 2000 rpm. The supernatant is discarded, and the cell pellets are resuspended with a minimal volume of sterile phosphate buffered saline (PBS). The mixture is then diluted with ammonium chloride and centrifuged. The supernatant is again discarded, and the remaining cell pellets are resuspended with a minimal volume of a tissue culture medium such as Minimal Essential Medium (MEM), available from KC Biological. The cell concentration is determined with a Coulter counter.

Interferon induction takes place in glass or plastic bottles. The induction medium contains MEM, 75mM Hepes (available from Calbiochem), 75mM Tricine (available from Sigma Chemical Co.), human agamma serum (18mg/ml), and gentamycin sulfate (from M.A. Bioproducts; 50 µg/ml). The cells are added to the induction vessels at a final concentration of 5 to 10 million cells per milliliter. The induction vessel is incubated in a 37°C water bath, and alpha interferon is added as a primer.

After two hours, Sendai virus is added to the induction mixture. This causes alpha interferon to be produced in the supernatant by the leukocytes. After 12-18 hours incubation time, the induction mixture is centrifuged. The cells are discarded, and the supernatant is then purified.

The crude interferon is chilled to 10°C or below in an ice bath. Five molar potassium thiocyanate is added to obtain a final concentration of 0.5M. This solution is stirred for 15 minutes, and then its pH is lowered to 3.3 by adding hydrochloric acid. The mixture is then centrifuged at 2800 rpm for 30 minutes, and the supernatant is discarded.

The pellets are then resuspended in 95% ethanol and are stirred for 15 minutes. This suspension is centrifuged at 2800 rpm for 20 minutes, and the pellets are discarded. The pH of the supernatant is then adjusted to 5.8 with sodium hydroxide. The mixture is stirred for 10 minutes, and then centrifuged at 2800 rpm for 20 minutes. The pellets

are discarded. The pH of the supernatant is then adjusted to 8 with sodium hydroxide. This solution is stirred for 10 minutes, followed by centrifugation at 2800 rpm for 20 minutes. The supernatant is discarded, and the pellets are resuspended with 0.5M potassium thiocyanate in a 0.1M sodium phosphate buffer. This suspension is stirred at 4°C.

Next, the suspension is centrifuged at 2800 rpm for 20 minutes, and the pellets are discarded. The pH of the supernatant is adjusted to 5.3 with hydrochloric acid. After stirring for 10 minutes and centrifugation, the pH of the supernatant is adjusted to 2.8 with hydrochloric acid, followed by further stirring for 20 minutes. This mixture is centrifuged at 2800 rpm, and the resulting pellet is purified human alpha-interferon.

The pellet is resuspended with 0.5M potassium thiocyanate in 0.1M sodium phosphate buffer, having a pH of 8.0. It is then dialyzed against PBS at 4°C, with two changes of PBS. This mixture is then centrifuged and the precipitate is discarded. The remaining purified alpha interferon is sterilized by filtration through a 0.2 µm filter. A human alpha-interferon is produced in accordance with this procedure by Immuno Modulators Laboratories, Inc., Stafford, Texas, and sold under the Registered Trade Mark Agriferon for use in cattle and the Registered Trade Mark Equiferon for use in horses.

Other procedures known to those skilled in the art are available for making interferons, such as human alpha-interferon and human gamma-interferon. For example, U.S. Patents 4,376,821 and 4,460,685 disclose methods of making human gamma-interferon. A method of making bovine fibroblast (beta) interferon is disclosed in applicant's U.S. patent 4,462,985.

Interferon Dosage Formulations

(1) Lozenge

A starch gel-based lozenge containing interferon is prepared by combining 150 grams of sucrose, 550 ml phosphate buffered saline, and 250 grams of a cold-water-soluble starch such as that described in U.S. Patent 4,465,702, heating that mixture with stirring to a temperature of 75°C, cooling the mixture to 30°C and thereafter blending into the paste-like mass 50 ml of phosphate buffered saline PBS containing human alpha interferon at a concentration of 250 IU/ml. The mixture is then formed into multiple portions of 5 to 10 grams each which set upon standing under drying conditions to a starch candy gel-like consistency. The lozenges thereby produced can be administered to a patient singly or in combination. The patient is instructed to hold the lozenge in his mouth until it is completely dissolved to release the interferon component for contact with the oral mucosa.

(2) Chewable Vitamin

A chewable vitamin formulation is prepared, for example, according to the description of U.S. Patent 3,857,939 by coating one or more components thereof prior to tableting with an interferon solution in an amount sufficient to provide 1 to 1500 units of interferon in each chewable vitamin tablet.

(3) Effervescent Tablet

A tableting mixture comprising a pharmaceutically acceptable alkali metal carbonate or bicarbonate, an organic acid such as citric acid, human interferon (preferably dispersed on a suitable organic or inorganic carrier therefor) in an amount sufficient to provide a per tablet dose of 1 to 1500 IU of interferon per dose, and further including suitable tableting excipients such as lubricants and binders, is compressed into a unitary dosage form of interferon. The compressed tablet effervesces upon contact with water to release interferon to the resulting buffered solution. The dosage of interferon is readily available in solution for contact with the oral pharyngeal mucosa of a patient in need of said dosage of interferon.

Human Treatment With Exogenous Human Alpha-Interferon

Human patients were treated with human alpha-interferon in the therapy of acute rheumatoid arthritis, multiple sclerosis, asthma, acne, malignant lymphoma, mesothelioma, and apthous stomatitis. Therapy consisted of oral administration of 1,6 u/kg (0.7 IU per lb.) of patient body weight twice daily, once in the morning and once in the evening. None of the patients noted any fever or anorexia associated with the administration of alpha interferon. Interferon was administered in a buffered solution having a concentration such that a single dosage could be administered in a volume of about 1 to about 20 ml of liquid. Each patient generally retained the interferon solution in his mouth for a period of time up to about one minute. After that time the solution was either swallowed or discharged from the patient's mouth.

Two patients suffering from rheumatoid arthritis were treated -- a Caucasian male age 44 and a Caucasian female age 44. The male patient was pain free in 7 days, and the female was pain free in 10 days. They were both continued on the oral interferon for 21 days total and have remained asymptomatic.

It has been found that recurrence of a treated arthritic condition can be minimized if treatment in accordance with the present invention is continued over a period of up to about three months.

A 30-year-old Caucasian female nurse afflicted with multiple sclerosis and who had had an extensive neurologic workup at City of Hope Hospital in Los Angeles received treatment in accordance with the present invention for 21 days. The patient has had no recurrence of her neurologic symptoms for the past nine months.

A 42-year-old Caucasian male diagnosed to have a malignant lymphoma had completed chemotherapy with dismal results and was considered terminal. He was treated for three weeks with oral interferon. Six months after starting treatment he was released by his oncologist as free of the disease.

An 82-year-old Caucasian female was diagnosed to have mesothelioma. Presently there is no effective treatment for that disease and only a 9-month average survival rate is predicted. During her treatment with human alpha-interferon she had thoracentesis on two occasions for plural effusion. Otherwise, the patient has been active and has survived for 43 months.

A 32-year-old Asian male with apthous stomatitis was treated for two weeks with human alpha-interferon in accordance with the present invention. There has been no recurrence of the ulcers over the last six months since treatment was completed.

BKC is a 29 year-old Caucasian female and KKJ is a 20 year-old Caucasian female. Both are afflicted by acne-like skin blemishes at the time of their monthly menstrual cycle. Oral human alpha-interferon given at about 2,3 u/kg (1 unit/lb) of body weight for 3 days prior to the time of their cycle reduces the severity and number of skin blemishes.

Claims

1. A composition comprising interferon and a pharmaceutically acceptable carrier therefor, in an effervescent tablet form adapted for dissolution in water to form a mouthwash or gargle formulation for human patient use for stimulating an immunotherapeutic response in said patient, said effervescent tablets containing 1 to 1500 IU of interferon.

2. A composition comprising interferon, starch and sucrose in a solid dosage form defined for buccal use by a human patient for stimulating an immunotherapeutic response in said patient, said solid dosage form comprising 1 to 1500 IU of interferon and a pharmaceutically acceptable carrier therefor, said solid dosage form adapted for dissolving in contact with saliva in the patient's mouth to release the interferon essentially for contact with the patient's oral and pharyngeal mucosa.

3. A composition according to claim 2 wherein said solid dosage form is a lozenge.

4. A composition according to claims 1, 2 or 3, wherein the interferon is alpha-interferon.

5. A composition according to claim 4, wherein the alpha-interferon is human alpha-interferon.

6. A method of manufacturing an interferon composition in solid dosage form defined for dissolving in contact with saliva in a patient's mouth and releasing said interferon for contact essentially with the oral and pharyngeal mucosa of said patient to stimulate an immunotherapeutic response, characterized by combining 1 to 1500 IU of interferon and a pharmaceutically acceptable carrier therefor.

7. A method according to claim 6, wherein the interferon is alpha-interferon.

8. A method according to claim 7, wherein the alpha-interferon is human alpha-interferon.

9. A method according to claims 6 to 8, wherein the pharmaceutically acceptable carrier comprises starch.

10. Use of interferon for the manufacture of a medicament in a solid dosage form defined for buccal use by a human patient, said solid dosage form adapted for dissolving in contact with saliva in the patient's mouth to release the interferon essentially for contact with the patient's oral and pharyngeal mucosa for stimulating an immunotherapeutic response in said patient, said solid dosage form comprising interferon and a pharmaceutically acceptable carrier therefor, and providing 0.022 to 11 IU of interferon per kg (0.01 to 5 IU/lb) of patient body weight.

11. Use of interferon for the manufacture of a medicament in an effervescent tablet form adapted for dissolution in water to form a mouthwash or gargle formulation for human patient use for stimulating a immunotherapeutic response in said patient, said effervescent tablet providing on dissolution 0.022 to 11 IU of interferon per kg (0.01 to 5 IU/lb) of patient body weight.

12. A use according to claim 10, wherein the solid dosage form is manufactured to provide 0.22 to 8.8 IU of interferon per kg (0.1 to 4 IU/lb) of patient body weight.

13. A use according to claim 10, wherein the solid dosage form is manufactured to provide 0.22 to 3.3 IU of interferon per kg (0.1 to 1.5 IU/lb) of patient body weight.

14. The use according to claim 10, where the solid dosage form is manufactured to provide 1.1 to 3.3. IU of interferon per kg (0.5 to 1.5 IU/lb) of patient body weight.

15. Use of alpha-interferon for the manufacture of a medicament of claim 10 to 14.

16. Use of human alpha-interferon for the manufacture of a medicament of claim 15.

17. Use of interferon in accordance with claims 10 to 16, for the manufacture of a medicament for the treatment of an autoimmune disorder consisting of multiple sclerosis, rheumatoid arthritis, nasal solar dermatitis, stomatitis and lupus erythematosus.

18. Use of interferon in accordance with claims 10 to 16, for the manufacture of a medicament for treatment of a neoplastic disease consisting of malignant lymphoma, melanoma, mesothelioma, Burkitt lymphoma and nasopharyngeal carcinoma.

19. Use of interferon in accordance with claims 10 to 16, for the manufacture of a medicament for treatment of a neoplastic disease consisting of Hodgkins disease and leukemia.

20. Use of interferon in accordance with claims 10 to 16, for the manufacture of a medicament for the treatment of acne.

21. Use of interferon in accordance with claims 10 to 16, for the manufacture of a medicament for the treatment of asthma.

22. Use of interferon in accordance with claims 10 to 16, for the manufacture of a medicament for the treatment of a viral infection selected from the group consisting of human rhinovirus, herpes simplex I virus, herpes simplex II virus, viral myocarditis and HTLV III virus (AIDS).

23. Use of interferon in accordance with claims 10 to 16, for the manufacture of a medicament for stimulating an immunotherapeutic response in a patient afflicted with AIDS.

Patentansprüche

1. Zusammensetzung, enthaltend Interferon und einen pharmazeutisch annehmbaren Träger dafür in Brausetablettenform, die sich zum Auflösen in Wasser unter Ausbildung einer Mundspül- oder Gurgelformulierung zur Erzeugung einer immuntherapeutischen Reaktion beim Menschen eignet, wobei die Brausetabletten 1 bis 1500 IE Interferon enthalten.

2. Zusammensetzung, enthaltend Interferon, Stärke und Saccharose in fester Darreichungsform zur buccalen Anwendung beim Menschen für die Erzeugung einer immuntherapeutischen Reaktion, wobei die feste Darreichungsform 1 bis 1500 IE Interferon und einen pharmazeutisch annehmbaren Träger dafür enthält und dazu geeignet ist, sich in Berührung mit Speichel im Munde des Patienten aufzulösen, um das Interferon im wesentlichen zur Berührung mit der Schleimhaut der Mundhöhle und des Rachenraumes des Patienten freizusetzen.

3. Zusammensetzung gemäß Anspruch 2, wobei die feste Darreichungsform eine Pastille ist.

4. Zusammensetzung gemäß Anspruch 1, 2 oder 3, wobei das Interferon α-Interferon ist.

5. Zusammensetzung gemäß Anspruch 4, wobei das α-Interferon α-Interferon vom Menschen ist.

6. Verfahren zur Herstellung einer Interferonzusammensetzung in fester Darreichungsform, die zur Auflösung in Berührung mit Speichel in der Mundhöhle des Menschen und zum Freisetzen des Interferons zur Berührung mit im wesentlichen der Schleimhaut der Mundhöhle und des Rachenraumes eines Patienten bestimmt ist, um eine immuntherapeutische Reaktion zu erzeugen, **dadurch gekennzeichnet,**
daß man 1 bis 1500 IE Interferon und einen pharmazeutisch annehmbaren Träger dafür miteinander vermischt.

7. Verfahren gemäß Anspruch 6, wobei das Interferon α-Interferon ist.

8. Verfahren gemäß Anspruch 7, wobei das α-Interferon α-Interferon des Menschen ist.

9. Verfahren gemäß den Ansprüchen 6 bis 8, wobei der pharmazeutisch annehmbare Träger

Stärke enthält.

10. Verwendung von Interferon zur Herstellung eines Arzneimittels in fester Darreichungsform, die für die buccale Anwendung beim Menschen bestimmt ist, wobei die feste Darreichungsform dazu geeignet ist, sich in Berührung mit Speichel in der Mundhöhle des Patienten aufzulösen, um das Interferon im wesentlichen zur Berührung mit der Schleimhaut der Mundhöhle und des Rachenraumes des Patienten freizusetzen, um eine immuntherapeutische Reaktion bei dem Patienten zu erzeugen, wobei die feste Darreichungsform Interferon und einen pharmazeutisch annehmbaren Träger dafür enthält, und um 0,022 bis 11 IE Interferon je kg Körpergewicht des Patienten (0,01 bis 5 IE/Pfund) zu liefern.

11. Verwendung von Interferon zur Herstellung eines Arzneimittels in Brausetablettenform, die sich zur Auflösung in Wasser unter Ausbildung einer Mundspül- oder Gurgelformulierung zur Erzeugung einer immuntherapeutischen Reaktion beim Menschen eignet, wobei die Brausetablette nach der Auflösung 0,022 bis 11 IE Interferon je kg Körpergewicht des Patienten (0,01 bis 5 IE/Pfund) liefert.

12. Verwendung gemäß Anspruch 10, wobei die feste Darreichungsform hergestellt wird, um 0,22 bis 8,8 IE Interferon je kg Körpergewicht des Patienten (0,1 bis 4 IE/Pfund) zu liefern.

13. Verwendung gemäß Anspruch 10, wobei die feste Darreichungsform hergestellt wird, um 0,22 bis 3,3 IE Interferon je kg Körpergewicht des Patienten (0,1 bis 1,5 IE/Pfund) zu liefern.

14. Verwendung gemäß Anspruch 10, wobei die feste Darreichungsform hergestellt wird, um 1,1 bis 3,3 IE Interferon je kg Körpergewicht des Patienten (0,5 bis 1,5 IE/Pfund) zu liefern.

15. Verwendung von α-Interferon zur Herstellung eines Arzneimittels gemäß Anspruch 10 bis 14.

16. Verwendung von α-Interferon des Menschen zur Herstellung eines Arzneimittels gemäß Anspruch 15.

17. Verwendung von Interferon gemäß Ansprüchen 10 bis 16 zur Herstellung eines Arzneimittels zur Behandlung einer Autoimmunstörung in Form von multipler Sklerose, rheumatoider Arthritis, Nasensonnenbrand, Stomatitis und Schmetterlingsflechte.

18. Verwendung von Interferon gemäß Ansprüchen 10 bis 16 zur Herstellung eines Arzneimittels für die Behandlung einer neoplastischen Krankheit in Form von malignem Lymphom, Melanom, Mesotheliom, Burkitt-Lymphom und Nasen-Rachen-Carcinom.

19. Verwendung von Interferon gemäß Ansprüchen 10 bis 16 zur Herstellung eines Arzneimittels für die Behandlung einer neoplastischen Krankheit in Form der Hodgkinschen Krankheit und der Leukämie.

20. Verwendung von Interferon gemäß Ansprüchen 10 bis 16 zur Herstellung eines Arzneimittels zur Behandlung von Akne.

21. Verwendung von Interferon gemäß Ansprüchen 10 bis 16 zur Herstellung eines Medikaments zur Behandlung von Asthma.

22. Verwendung von Interferon gemäß Ansprüchen 10 bis 16 zur Herstellung eines Arzneimittels für die Behandlung einer Virusinfektion in Form von Infektionen durch den Rhinovirus des Menschen, den Herpes-Simplex-I-Virus, den Herpes-Simplex-II-Virus, sowie der viralen Myocarditis und Infektionen durch den HTLV-III-Virus (AIDS).

23. Verwendung von Interferon gemäß Ansprüchen 10 bis 16 zur Herstellung eines Arzneimittels zur Hervorrufung einer immuntherapeutischen Reaktion bei einem AIDS-Patienten.

Revendications

1. Composition comprenant de l'interféron et un support pharmaceutiquement acceptable pour ce dernier, en comprimé effervescent conçu pour être dissous dans de l'eau pour former une formulation pour lavage de bouche ou gargarisme à utiliser par un patient humain pour stimuler une réponse immuno-thérapeutique chez ledit patient, lesdits comprimés effervescents contenant 1 à 1500 UI d'interféron.

2. Composition comprenant de l'interféron, de l'amidon et du saccharose sous une forme galénique solide, conçue pour une utilisation buccale, pour un patient humain, pour stimuler une réponse immuno-thérapeutique chez ledit patient, ladite forme galénique solide comprenant 1 à 1500 UI d'interféron et un support pharmaceutiquement acceptable pour ce dernier, ladite forme galénique étant conçue pour se dissoudre au contact de la salive dans la bouche du patient pour libérer l'interféron es-

sentiellement pour le mettre en contact avec la muqueuse orale et pharyngée du patient.

3. Composition selon la revendication 2, dans laquelle ladite forme galénique solide est une pastille.

4. Composition selon les revendications 1, 2 ou 3, dans laquelle l'interféron est l'alpha-interféron.

5. Composition selon la revendication 4, dans laquelle l'alpha-interféron est un alpha-interféron humain.

6. Procédé de fabrication d'une composition d'interféron sous forme galénique solide, conçue pour se dissoudre au contact de la salive dans la bouche d'un patient et pour libérer ledit interféron pour le mettre en contact essentiellement avec la muqueuse orale et pharyngée dudit patient, afin de stimuler une réponse immuno-thérapeutique, caractérisé en ce que l'on combine 1 à 1500 UI d'interféron et un support pharmaceutiquement acceptable pour ce dernier.

7. Procédé selon la revendication 6, dans lequel l'interféron est l'alpha-interféron.

8. Procédé selon la revendication 7, dans lequel l'alpha-interféron est un alpha-interféron humain.

9. Procédé selon les revendications 6 à 8, dans lequel le support pharmaceutiquement acceptable comprend de l'amidon.

10. Utilisation d'interféron pour fabriquer un médicament sous une forme galénique solide, à usage buccal, pour un patient humain, ladite forme galénique solide étant conçue pour se dissoudre au contact de la salive dans la bouche d'un patient et pour libérer ledit interféron pour le mettre essentiellement en contact avec la muqueuse orale et pharyngée du patient, afin de stimuler une réponse immuno-thérapeutique chez ledit patient, ladite forme galénique solide comprenant de l'interféron et un support pharmaceutiquement acceptable pour ce dernier et apportant 0,022 à 11 UI d'interféron par kg (0,01 à 5 UI/lb) de poids corporel du patient.

11. Utilisation d'interféron pour fabriquer un médicament en comprimé effervescent conçu pour être dissous dans de l'eau afin de former une formulation pour lavage de bouche ou gargarisme à utiliser par un patient humain pour stimuler une réponse immuno-thérapeutique chez ledit patient, ledit comprimé effervescent apportant 0,022 à 11 UI d'interféron par kg (0,01 à 5 UI/lb) de poids corporel du patient.

12. Utilisation selon la revendication 10, dans laquelle la forme galénique solide est fabriquée de façon à apporter 0,22 à 8,8 UI d'interféron par kg (0,1 à 4 UI/lb) de poids corporel du patient.

13. Utilisation selon la revendication 10, dans laquelle la forme galénique solide est fabriquée de façon à apporter 0,22 à 3,3 UI d'interféron par kg (0,1 à 1,5 UI/lb) de poids corporel du patient.

14. Utilisation selon la revendication 10, dans laquelle la forme galénique solide est fabriquée de façon à apporter 1,1 à 3,3 UI d'interféron par kg (0,5 à 1,5 UI/lb) de poids corporel du patient.

15. Utilisation d'alpha-interféron pour fabriquer un médicament selon les revendications 10 à 14.

16. Utilisation d'alpha-interféron humain pour fabriquer un médicament selon la revendication 15.

17. Utilisation d'interféron selon les revendications 10 à 16, pour fabriquer un médicament pour le traitement d'une maladie auto-immune, consistant en la sclérose en plaques, la polyarthrite rhumatoïde, l'actinite solaire nasale, la stomatite et le lupus érythémateux.

18. Utilisation d'interféron selon les revendications 10 à 16, pour fabriquer un médicament pour le traitement d'une maladie néoplasique consistant en le lymphome malin, le mélanome, le mésothéliome, la tumeur de Burkitt et le cancer du rhino-pharynx.

19. Utilisation d'interféron selon les revendications 10 à 16, pour fabriquer un médicament pour le traitement d'une maladie néoplasique consistant en la maladie de Hodgkin et la leucémie.

20. Utilisation d'interféron selon les revendications 10 à 16, pour fabriquer un médicament pour le traitement de l'acné.

21. Utilisation d'interféron selon les revendications 10 à 16, pour fabriquer un médicament pour le traitement de l'asthme.

22. Utilisation d'interféron selon les revendications 10 à 16, pour fabriquer un médicament pour le traitement d'une infection virale choisie dans le groupe constitué par le rhinovirus humain, l'herpèsvirus simple I, l'herpèsvirus simple II, la myocardite virale et le virus HTLV III (SIDA).

23. Utilisation d'interféron selon les revendications 10 à 16, pour fabriquer un médicament pour stimuler la réponse immuno-thérapeutique d'un patient souffrant du SIDA.